Feasibility of Combined Unipolar and Bipolar Voltage Maps to Improve Sensitivity of Endomyocardial Biopsy

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Background—Endomyocardial biopsy (EMB) has a low sensitivity. Electroanatomic voltage mapping (EVM) is effective in guiding EMB thanks to its ability in identifying and locating low-voltage regions. The analysis of unipolar EVM can correlate with epicardial pathological involvement. We evaluated the unipolar EVM in EMB areas to determine whether it can increase EMB sensitivity in diagnosing epicardial diseases.

Methods and Results—We performed endocardial bipolar EVM-guided EMBs in 29 patients and we analyzed unipolar EVM at withdrawal sites. Eighty myocardial samples were collected (mean, 2.8±0.9; median, 3 fragments per patient) and 60 were suitable for histological analysis. Ten specimens (17%) were collected from an area with discordant normal bipolar/low-voltage unipolar EVM and they were diagnostic or suggestive for arrhythmogenic right ventricular dysplasia/cardiomyopathy in 6 patients, for myocarditis and sarcoidosis in 1 patient each. Six samples (10%) were collected from an area with discordant low-voltage bipolar/normal unipolar EVM and they showed nonspecific features. The sensitivity of unipolar EVMs for a diagnostic biopsy finding EMB was significantly higher compared with bipolar EVMs analyzed according to samples (P<0.01) and patients (P=0.008). The specificity of unipolar EMB was better than bipolar EMB when analyzed for all samples (P=0.0014) but the difference did not reach statistical significance when analyzed by patient (P=0.083). The diagnostic yield was 63.3% for the bipolar and 83.3% for the unipolar EVM.

Conclusions—These findings suggest that use of a combined bipolar/unipolar map may be able to improve the diagnostic yield of endomyocardial ventricular biopsy. **(*Circ Arrhythm Electrophysiol*. 2015;8:625-632. DOI: 10.1161/CIRCEP.114.002216.)**

Key Words: arrhythmogenic right ventricular dysplasia ■ myocarditis

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According to current guidelines, endomyocardial biopsy (EMB) may be considered in the setting of suspected arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) and of unexplained ventricular arrhythmias (Class of Recommendation IIb, Level of Evidence C).[1] Furthermore, EMB is of primary importance to make a definitive diagnosis of ARVD/C,[2,3,4] the gold standard for the diagnosis of myocarditis[5] and often the only way to differentiate cardiac sarcoidosis from other forms of cardiomyopathies.[6]

Conventionally, myocardial samples have been taken from the interventricular septum to minimize the risk of perforation. Nevertheless, the focal nature of the diseases and the only rare involvement of the interventricular septum have significantly limited the sensitivity of EMB. Starting from 2007, the conventional approach has been replaced by the electroanatomic voltage mapping (EVM)–guided approach, improving the diagnostic sensitivity of EMB.[7–9]

All the published studies about EMB guided by EVM used bipolar voltage mapping. Nevertheless, it was demonstrated that the epicardial substrate in patients with ARVD/C is frequently more extensive than the endocardial one shown by bipolar endocardial EVM.[10] Polin et al[11] demonstrated that the epicardial involvement may be accurately identified by

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WHAT IS KNOWN

- Bipolar electroanatomic voltage mapping (EVM) improves diagnostic sensitivity of endomyocardial biopsy when used to guide withdrawal site.
- Unipolar EVM may accurately identify the arrhythmogenic right ventricular dysplasia/cardiomyopathy epicardial involvement, avoiding the potential risks associated with an epicardial mapping.

WHAT THE STUDY ADDS

- Unipolar EVM helps to detect intramyocardial and epicardial involvement, especially when bipolar EVM is normal or minimally affected.
- Unipolar EVM analysis should be performed in the hypothesis of an epicardial or intramyocardial involvement and the combined bipolar/unipolar map may be used to guide endomyocardial biopsy.

unipolar EVM, avoiding the potential risks associated with an epicardial mapping.

In this study, we evaluated the unipolar EVM in biopsy areas to determine whether it can further increase EMB sensitivity in diagnosing diseases that are frequently epicardial or intramyocardial.

Methods

Patient Population

We studied 29 consecutive patients (24 men; mean age, 37±13 years) who underwent EMB between January 2010 and April 2014 according to current American Heart Association/American College of Cardiology Foundation/European Society of Cardiology indications.[1]

All patients underwent a noninvasive evaluation with history, physical examination, laboratory tests, 12-lead ECG, and 2-dimensional echocardiography. Gadolinium-enhanced cardiac magnetic resonance imaging was performed in 28 patients (97%), exercise testing in 17 (59%), and coronary angiography in 12 patients (41%). All patients gave informed consent to all tests and procedures performed during hospitalization. The study was approved by the Internal Scientific Committee.

Electroanatomic Mapping

All patients underwent right ventricle (RV) electroanatomic mapping performed with CARTO system (Biosense Webster) during sinus rhythm. At least 150 mapping points were sampled with an irrigated-tip Navi-Star catheter. In 15 of 29 (52%) patients, we used a catheter with a contact sensor to provide contact information during signal acquisition. A contact of ≥10 g considered adequate. In 19 patients (66%), intracardiac echocardiography (ICE) was used because to give a preliminary view of ventricle anatomy and confirmation of adequate contact during signal acquisition (Figure 1).

During the mapping procedure, we analyzed bipolar electrograms, whereas unipolar map was automatically created and analyzed after the biopsy was taken, and before biopsy report knowledge. Reference values for identifying normal endocardial bipolar and unipolar signals were defined as >1.5 and >5.5 mV, respectively.[9,12]

The anatomic distribution of the pathological areas was evaluated by dividing RV voltage map into 5 segments, such as outflow, anterolateral, inferoposterior, apical, and septal.[6]

Endomyocardial Biopsy

RV endomyocardial bioptic samples were obtained through the right femoral vein via a disposable bioptome (Bipal, Biosense Webster) introduced into a steerable sheath (Agilis NxT, St. Jude Medical).

The bioptome catheter was always displayed into the CARTO system through the Advanced Catheter Localization technology, that permits the localization of all catheters inside the heart thanks to the measurement of changes in the basal electric range generated by patches initially put on the patient's chest and back.

We put a small screw into the adapter of the bioptome handle and we pinched it with a couple of alligator clips, creating an electric dipole. The end of the electric cables was then connected to the CARTO

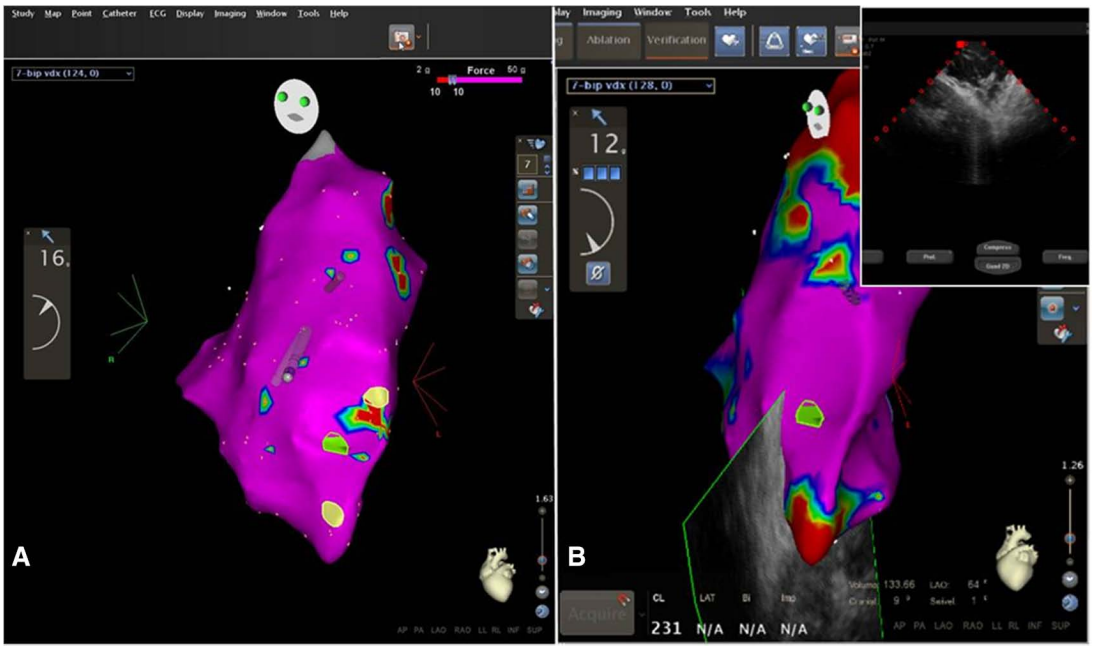

Figure 1. A, Right ventricular (RV) force map with the cutoff set at 10 g **B**, CARTO Sound image during reconstruction of endocardial unipolar voltage map (cutoff at 5.5 mV); the intracardiac echocardiography allows to visualize the RV wall and to check the mapping catheter contact.

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system and visualized as any other catheter. In addition to fluoroscopy, the correct position of the bioptome was, therefore, checked both through the CARTO system and through ICE (when available), (Figure I in the Data Supplement).

An EMB guided by EVM was performed in all patients who had an abnormal bipolar map. In every patient, at least 1 sample was obtained from an area with normal bipolar electrograms and one from an area with pathological bipolar electrograms. In patients with a normal bipolar EVM, EMB was randomly performed in conventional sites. The sites of biopsy were marked on the map (Movie 1in the Data Supplement).

Once we had the biopsy report, we correlated the bipolar and unipolar voltage map at the sampling sites and we matched the EVM results with biopsies.

Histology and Immunohistochemistry Analysis

For each patient, 2 to 3 samples were obtained for histology and immunohistochemistry then fixed in 10% phosphate-buffered formalin (pH 7.35), and embedded in paraffin. Histological analysis was performed as previously described.[6] In summary, 6 µm-thick serial sections were cut and stained with hematoxylin–eosin and Masson trichrome stain. Immunohistochemistry for the characterization of inflammatory infiltrates was performed using the following antibodies: CD3, CD20, and CD68 (Dako Corporation, Glostrup, Denmark).

In patients presenting histological evidence of fibrofatty replacement, a histomorphometric analysis was performed to calculate the extent of myocardial atrophy and fibrofatty replacement.

Statistical Analysis

Descriptive statistics are reported as mean±SD or median and interquartile Q1–Q3 range for skewed distributions in case of continuous variables, and as frequencies and percentages for categorical variables. Between-group comparisons were performed with the Mc Nemar Test or Wilcoxon signed-rank test.

Sensibility and Specificity and confidence interval (CI) 95% assuming the binomial distribution were computed and a McNemar test for the comparison between 2 methods was performed. All tests were 2-sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using the SAS 9.2 (SAS Institute, Inc, Cary, NC).

Results

Patient Population

The clinical characteristics of the study population are outlined in Table 1 and in Table I in the Data Supplement

Considering clinical and instrumental examinations data (including EMB analysis), the following diagnosis were made: ARVD/C in 9 (31%) patients, active myocarditis in 3 (10%), idiopathic dilated cardiomyopathy in 2 (7%), previous myocarditis in 2 (7%), cardiac sarcoidosis, idiopathic ventricular fibrillation, left ventricle noncompaction, mitochondrial cardiac disease 1 (3%) each. An idiopathic right ventricle outflow tract tachycardia diagnosis was formulated in 6 (21%) cases and nonspecific cardiac disease in 3 (10%) cases.

During hospitalization, a catheter ablation of VAs was performed in 19 (66%) patients, whereas an implantable cardiac defibrillator (ICD) was implanted in 2 cases.

Table 1. Study Population Features

	Patients (n=29)
Age, y	37±13
Male subjects	24/29 (83%)
Sustained VT, Syncope, or sudden death history	13/29 (45%)
12-lead ECG abnormalities	12/29 (41%)
LV ejection fraction, %	58±9
RV ejection fraction, %	46±9
cMRI pathological findings	21/28 (75%)
Previous ICD implantation	7/29 (24%)
Previous catheter ablation	6/29 (21%)

Values express as number of patients (%) or as mean±SD. cMRI indicates cardiac magnetic resonance imaging; ICD, implantable cardiac defibrillator; LV, left ventricle; RV, right ventricle; and VT, ventricular tachycardia.

Electroanatomic Voltage Mapping

Endocardial EVM was successfully acquired in all patients, with a mean number of sites sampled of 276±93 in a mean RV surface of 186.7±55.5 cm^2.

The bipolar EVM analysis documented a completely normal bipolar EVM in 12 (41%) patients while revealed at least 1 low-voltage area in 17 (59%) patients; in these patients, the mean bipolar low-voltage areas involved 8.1±6.9% of the whole surface. The most frequently involved regions were outflow tract (13/17, 76%), anterolateral segment (7/17, 41%), inferoposterior wall (3/17, 18%), RV apex and septal wall (1/17 each, 6%).

The unipolar EVM analysis documented at least 1 low-voltage area in 21 patients (72%) with a mean unipolar low-voltage areas corresponding to 33.3±29.7% of the whole surface. The areas most frequently presenting unipolar low voltages were outflow tract (18/21, 86%), anterolateral wall (15/21, 71%), apex (8/21, 38%), inferoposterior wall (7/21, 33%), and septum (3/21, 14%). Comparing bipolar with unipolar EVM, the latter revealed a significantly larger area of low-voltage abnormality ($P<0.01$) and a significantly more frequent involvement of outflow tract ($P=0.031$), anterolateral wall ($P<0.01$), and apex ($P<0.01$).

Endomyocardial Biopsy

A total of 80 myocardial samples were collected in 29 patients (median, 3; interquartile range, 2–3). Fifty-four (68%) myocardial samples were performed in a normal bipolar voltage area, whereas 26 were obtained from bipolar low-voltage areas. The most frequent sites of biopsy were septum, 40 (50%); anterolateral free wall, 14 (18%); apex, 13 (16%); right ventricle outflow tract, 8 (10%); and inferoposterior wall, 5 (6%). No procedural complications were documented.

Sixty myocardial samples (75%) were suitable for histological analysis.

Biopsy samplings showed myocardial fibrofatty replacement diagnostic for ARVD/C in 6 specimens (3 patients), whereas 7 specimens (6 patients) satisfied Task Force requirements for a borderline diagnosis of ARVD/C[2] (Figure 2; Figure II in the Data Supplement).

Six specimens (3 patients) were consistent with active myocarditis according to Dallas criteria[13,14] (Figure 3), 1 specimen was diagnostic for cardiac sarcoidosis,[15] 1 was consistent with mitochondrial cardiomyopathy,[16] and 1 with idiopathic dilated cardiomyopathy.[17]

Nonspecific microscopic features were observed in 19 specimens (13 patients). Finally, in 19 specimens (13 patients), no pathological features were found.

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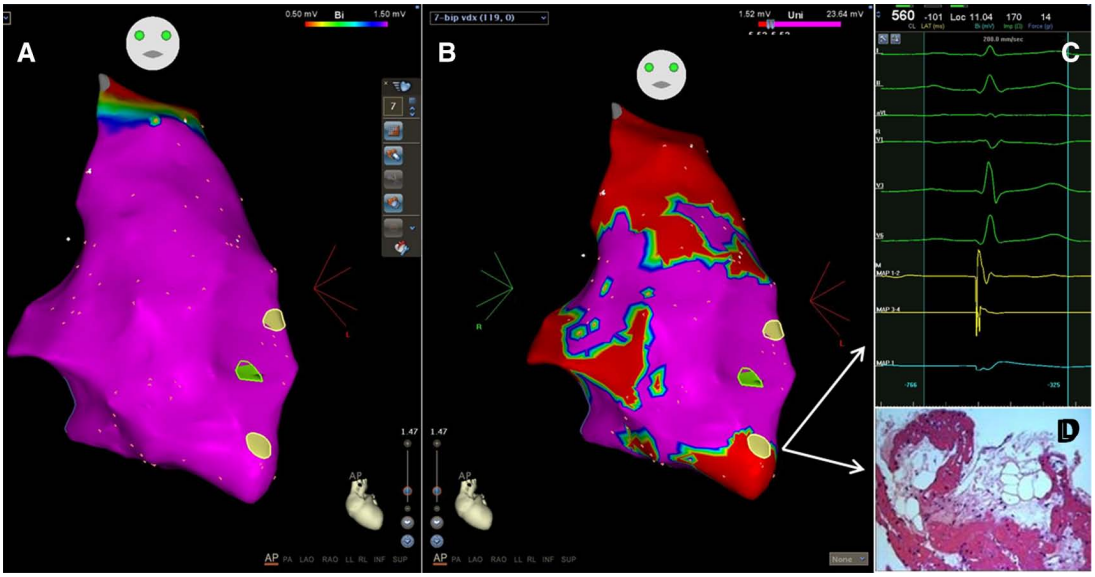

Figure 2. A, Endocardial bipolar voltage map of a patient undergoing endomyocardial biopsy for a suspicion of arrhythmogenic right ventricular dysplasia/cardiomyopathy; the map is completely normal. **B**, Endocardial unipolar voltage map of the same patient; in this case areas of low voltage (red) are evident at right ventricle outflow tract, apex, and peritricuspidalic sites. **C**, Discordant normal bipolar (yellow) and low-voltage unipolar (light blue) electrograms at withdrawal site. **D**, The biopsy performed at the apex showed fibrofatty replacement corresponding to 30% of the whole tissue.

Correlation Between Histological Features, Electroanatomic Mapping, and Definite Diagnosis

Analyzing bipolar and unipolar EVM at the site of biopsy, we found that 34 (57%) specimens were collected from a concordant bipolar/unipolar normal voltage area; 9 (15%) from a concordant bipolar/unipolar low-voltage area; 11 (18%) from an area with discordant bipolar normal voltage and unipolar low voltage; 6 (10%) from an area with discordant bipolar low voltage and unipolar normal voltage.

Table 2 correlates histological results of the 60 myocardial samples with the bipolar/unipolar EVMs at sites of withdrawal.

In summary, EMB satisfied the criteria for a definite diagnosis in 9 (31%) patients, whereas a histopathological suspicion of ARVD/C was described in 6 (21%). Between these 6 patients, the diagnosis of ARVD/C was then confirmed by genetic test in 2 cases, whereas in the remaining 4 patients the diagnosis was confirmed by clinical history and cardiac

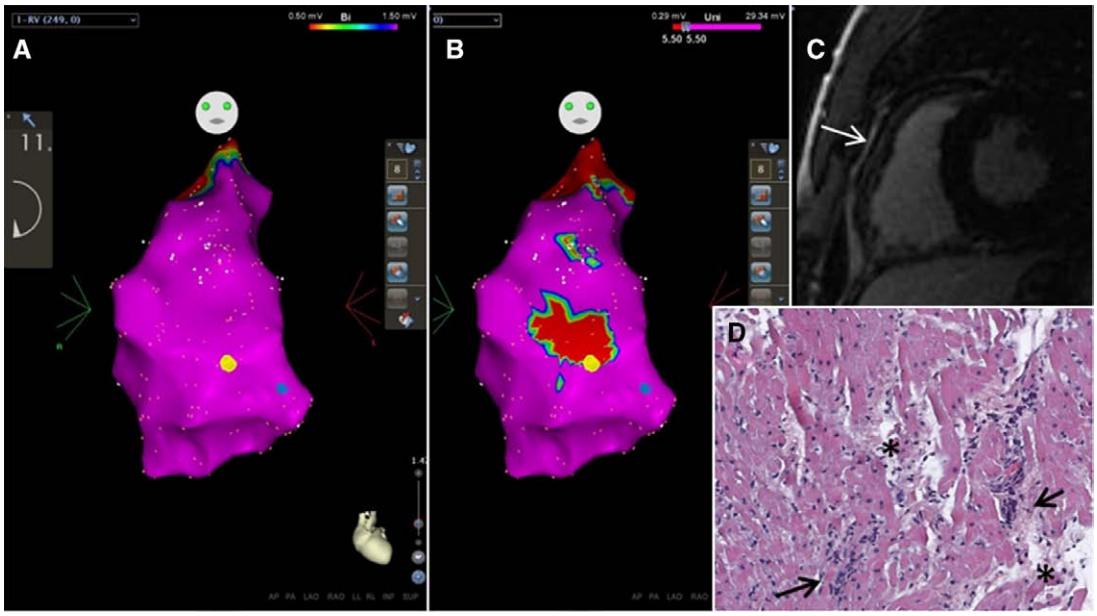

Figure 3. A and **B**, Bipolar (on the left) and unipolar (on the right) endocardial map of a patient with a bioptic diagnosis of active myocarditis. The yellow dot highlights the site of diagnostic biopsy sampling. The blue dot shows the site of normal biopsy sampling. **C**, Cardiac magnetic resonance imaging of the same patient. The arrow points out a subepicardial scar detected by delayed enhancementat the basis of the right ventricle outflow tract. **D**, Diffuse inflammatory infiltrates (arrows) associated with necrosis of adjacent myocytes (asterisks) consistent with the diagnosis of active myocarditis.

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Table 2. Bipolar/Unipolar Electroanatomic Voltage Mapping Analysis at Withdrawal Site of All Endomyocardial Biopsies

	Bip/Unip −/−	Bip/Unip +/+	Bip/Unip −/+	Bip/Unip +/−	Bip+	Unip+
n Samples	35 (58%)	9 (15%)	10 (17%)	6 (10%)	15 (25%)	19 (32%)
ARVD/C	0	6 (67%)	0	0	6 (40%)	6 (32%)
ARVD/C borderline	0	0	7 (70%)	0	0	7 (37%)
Myocarditis	4 (12%)	0	2 (20%)	0	0	2 (11%)
Sarcoidosis	0	0	1 (10%)	0	0	1 (5%)
IDCM	0	1 (1%)	0	0	1 (7%)	1 (5%)
Mitochondrial Proliferation	0	1 (1%)	0	0	1 (7%)	1 (5%)
Non specific	12 (34%)	1 (1%)	0	6 (100%)	7 (47%)	1 (5%)
Normal	19 (56%)	0	0	0	0	0

ARVD/C indicates arrhythmogenic right ventricular dysplasia/cardiomyopathy; and IDCM, idiopathic dilated cardiomyopathy.

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imaging major criteria. Both patients with a positive genetic test were carriers of the same nonsense PKP2 mutation (c.2011delC and p.K672R fs12X).[18]

Considering the site of biopsy, the diseased unipolar/normal bipolar sites were associated with a definite diagnosis in 8 patients (6 ARVD/C, 1 myocarditis, and 1 sarcoidosis). On the contrary, all biopsy samplings performed in areas of diseased bipolar/normal unipolar EVMs showed nonspecific features.

The sensitivity of unipolar EVMs for a definite diagnosis was significantly higher compared with bipolar EVMs considering both biopsy samples (unipolar SE, 81.8%; 95% CI, 60%–95% and bipolar SE, 36.4%; 95% CI, 17%–59%; *P*=0.014) and patients (unipolar SE, 86.7%; 95% CI, 60%–98% and bipolar SE, 40%; 95% CI, 16%–68%; *P*=0.008).

The specificity of unipolar EVM was better than bipolar EVM when analyzed for all samples (unipolar SP, 97.4%; 95% CI, 86%–99% and bipolar SP, 81.6%; 95% CI, 66%–92%; *P*=0.014) but the difference did not reach statistical significance when analyzed according to patients (unipolar SP, 92.7%; 95% CI, 66%–99% and bipolar SP, 71.4%; 95% CI, 42%–92%; *P*=0.083).

We also evaluated the diagnostic yield considering the number of concordant results (pathological bipolar or unipolar voltage mapping/pathological biopsy finding and vice versa) divided by the number of samples. For the 60 samples suitable for histological analysis, we had a value of 63.3% for the bipolar and of 83.3% for the unipolar voltage map.

Table 3 shows the definite histopathological diagnosis obtained in 15 patients with the bipolar/unipolar EVMs at biopsy sampling sites.

In Table II in the Data Supplement, we show in detail the sites of withdrawal, electroanatomic mapping, signal characteristics, and the definitive histological diagnosis.

Discussion

Main Findings

In our study, endocardial unipolar EVM has been used for the first time to characterize RV myocardial substrate in patients undergoing EMB. On the basis of our data, unipolar EMB was associated with increased sensitivity and specificity for the presence of diagnostic findings ≤98% and 99%, respectively.

These data could be explained considering that unipolar diseased areas are significantly larger than bipolar ones and that unipolar EVMs reveal areas of diseased myocardium even in case of a completely normal or minimally affected bipolar EVMs. Therefore, bipolar EVM only could underestimate the degree of abnormal myocardium, whereas unipolar EVM allows to detect cardiac diseases (eg, ARVD/C) that typically involve the epicardium and to identify the exact localization of pathological areas in multifocal diseases (eg, myocarditis).

Furthermore, unipolar EVM-guided EMB has a larger target area where a diagnostic sample can be performed; thus the technical chance to reach a diagnostic site may be improved by assessing both bipolar and unipolar EVM.

Table 3. Bipolar/Unipolar Electroanatomic Voltage Mapping Analysis at Withdrawal Site of Diagnostic Endomyocardial Biopsies

	Bip/Unip −/−	Bip/Unip +/+	Bip/Unip −/+	Bip/Unip +/−	Bip+	Unip+
ARVD/C	0	3 (20%)	0	0	3 (20%)	3 (20%)
ARVD/C borderline	0	0	6 (40%)	0	0	6 (40%)
Myocarditis	2 (13%)	0	1 (7%)	0	0	1 (7%)
Sarcoidosis	0	0	1 (7%)	0	0	1 (7%)
IDCM	0	1 (7%)	0	0	1 (7%)	1 (7%)
Mitochondrial Proliferation	0	1 (7%)	0	0	1 (7%)	1 (7%)
Total (15 pts)	2 (13%)	5 (33%)	8 (53%)	0	5 (33%)	13 (87%)

ARVD/C indicates arrhythmogenic right ventricular dysplasia/cardiomyopathy; and IDCM, idiopathic dilated cardiomyopathy.

EVM Mapping

In 2011, Polin et al published a pivotal work where they validated the use of unipolar EVM for identifying the presence and anatomic extent of epicardial low-voltage areas performing an endocardial mapping.[11] As, then it has become possible to acquire information about intramyocardial and epicardial substrate from a traditional endocardial mapping, avoiding the risk of epicardial mapping and having from the inside a picture of the full-thickness of the myocardial wall and not of the endocardium only. Obviously, the clinical implication of this technique is particularly important for cardiac diseases with a typical involvement toward the epicardium, such as ARVD/C.

We applied the unipolar mapping technique proposed by Polin et al[11] in patients undergoing EMB for suspected ARVD/C or unexplained VAs. First, our data confirmed that unipolar EVM reveals a significantly larger area of low voltages compared with bipolar EVM. Of interest, these bipolar/unipolar EVM discrepancies were mainly located in the free wall, infundibulum, and apex, thus in the most frequently involved regions of the triangle of dysplasia. Furthermore, the use of a mapping catheter enhanced with contact force sensing and the use of ICE make us more reliable about voltage map reconstruction.

Of interest, unipolar EVM map proved to have a high sensitivity and to be particularly useful in patients with suspected ARVD/C. As matter of fact, all biopsy samples showing myocardial fibrofatty replacement consistent with or suggestive for a histopathological diagnosis of ARVD/C were derived from a low-potential unipolar area. Besides in 4 of 9 ARVD/C patients, bipolar EVM was completely normal. These findings could be explained considering that ARVD/C is characterized by accumulation of fibrofatty scar tissue that may be confined to epicardial/midmural layers, sparing (or reaching focally) the endocardial region. Thus, unipolar EVM map may have highlighted epicardial disease and discordant unipolar diseased/bipolar healthy tissue could be expression of a minimal involvement of the substrate. Anyhow, unipolar EVM may provide an efficient antenna to detect patients presenting with arrhythmia preceding detectable anatomic changes and that have a sudden death risk.

As in ARVD/C, unipolar EVM seems to be an indispensable tool also in myocarditis. Maccabelli et al[19] showed that endocardial unipolar voltage reduction in the absence of bipolar abnormalities is indicative of epicardial or midwall scar. Endocardial unipolar EVM is able to detect thicker scars extending from the subepicardium to the midwall layers of the ventricle. Accordingly, in our series we had 1 patient with a biopsy showing myocarditis that had normal bipolar EVM and pathological unipolar EVM.

Endomyocardial Biopsy

EMB is the gold standard for in vivo diagnosis of specific myocardial disorders and is often considered when the pathogenesis of myocardial disorders cannot be determined by noninvasive testing. Nevertheless, because of the invasiveness of the procedure and complication risks, the indications for EMB have been a subject of debate and the practice varies widely even among major cardiovascular centers. The main issue related to EMB is that false-negative results are possible, especially in case of multifocal/microfocal or localized diseases.

In a recent article, Bennet et al[20] analyzed retrospectively 851 patients undergoing a standard fluoroscopy-guided EMB. From their data, EMB provided a diagnosis or altered the patient's clinical course in 25.5% and 22.7% of cases, respectively. The authors suggested a low impact of EMB in chronic cardiomyopathies that respond to usual care. In 2005, Corrado et al[21] showed that performing EMB by a traditional approach resulted in nondiagnostic findings in 25% of ARVD/C patients with abnormal bipolar EVM. In a study of 26 patients in whom cardiac sarcoidosis was strongly suspected on the basis of clinical diagnostic criteria, noncaseating granulomata were found only in 19% of the patients, confirming that EMB sensitivity for sarcoidosis is 20% to 30%.[1] Finally, in myocarditis the sensitivity of EMB depends on the duration of symptoms, but generally the yield is lower (10%–35%).[1] Furthermore, myocarditis is typically a multifocal or microfocal disease, it often involves epicardium or the midwall sparing the endocardium, and it has a broad spectrum of histological findings depending on the time, in which the biopsy is performed.[5,9,22,23]

Instead, with the use of advanced imaging technique, EMB diagnostic accuracy significantly increases. In the setting of suspected myocarditis, a cardiac magnetic resonance imaging–guided biopsy in the area of contrast enhancement brought the EMB diagnostic accuracy ≤90% both in active acute or in chronic myocarditis.[24] Recently, our group, for the first time, highlighted the role of EVM-guided EMB, showing that in patients with pathological RV bipolar electroanatomic map, myocardial samples obtained from low-voltage areas resulted diagnostic in 81% of patients with suspected ARVD/C[8] and allowed to properly differentiate patients affected by myocarditis from patients affected by ARVD/C.[7] Therefore, it is crucial to target the affected tissue as to improve the sensitivity of the EMB, especially in the setting of ARVD/C. EVM-guided EMB can be 1 simple solution for this challenge, but the bipolar map could be normal and the common sampling sites are usually the least and the last affected in ARVD/C or just 1 of many possibly affected areas in myocarditis. Unipolar map exposed us a new target to obtain EMB although the absence of abnormal bipolar EVM, and added new areas to reach.

Finally, we want to emphasize that the histological analysis of sample coming from normal bipolar/diseased unipolar areas showed myocardial atrophy <40% of the overall sample. Basso et al[25] demonstrated that myocardial atrophy should be regarded as the most important morphological parameter for the in vivo diagnosis of ARVD/C by EMB, with a diagnostic cutoff of cumulative residual myocardium of 59% (by selecting a 80% sensitivity and 95% specificity). Thus, our samples were evaluated just as borderline; the clinical history, cardiac imaging, and genetic test confirmed the diagnosis of ARVD/C in all these 6 patients. As Basso et al[25] emphasizes in their work, we agree that the final interpretation of EMB requires knowledge of their precise location as, for each analyzed tissue parameter, both sensitivity and specificity are different according to the sampling sites.

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Technical Aspects

In addition, we successfully used ICE imaging and the contact force feedback (once available) focusing endomyocardial samplings on selected RV areas and significantly improving histological outcome, even in presence of a focal or no low-voltage endocardial substrate. Moreover, the use of ICE permitted us to avoid sampling from thinner areas, increasing procedural safety.

Study Limitations

Our study has some obvious limitations. First of all, the analysis of the unipolar EVMs was performed after the biopsy was obtained; unipolar maps were, therefore, extrapolated post hoc and unipolar points of border zone were not confirmed. Thus, our results should be confirmed by a prospective randomized study.

Second, we analyzed a relative small number of patients, linked to the low prevalence in the general population of the diseases involved and to restrictive indications to EMB according to current guidelines. The small number of patients and of myocardial samples limited the power of the statistical analysis.

Furthermore, we performed epicardial mapping only in 5 patients, so that we do not have a statistic comparison between endocardial unipolar maps and epicardial maps at the sampling sites.

Finally, in this study we performed RV–EVM and EMB only but we think that its implications may be relevant in left ventricle substrate too. Further studies are needed to explore this hypothesis.

Conclusions

Unipolar EVM can help to detect myocardial disease because of its ability to detect intra and epicardial involvement, especially when bipolar EVM is normal or minimally affected.

Our findings suggest that analysis of the combined bipolar/unipolar map to guide EMB may help to improve the diagnostic yield. A prospective study is warranted.

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Disclosures

Dr Tondo has served as a member of the advisory board of Biosense Webster and has been consultant for St. Jude Medical. Dr Notarstefano is a consultant for Biosense Webster. Dr Natale received compensation for belonging to the speakers' bureau for St. Jude Medical, Boston Scientific, Medtronic, and Biosense Webster and has received a research grant from St. Jude Medical. He is a consultant for Biosense Webster. Dr Di Biase is a consultant for Hansen Medical, Biosense-Webster, and St. Jude Medical. He received speaker honoraria from Biotronik, EPI-EP, and Atricure. The other authors report no conflicts.

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Feasibility of Combined Unipolar and Bipolar Voltage Maps to Improve Sensitivity of Endomyocardial Biopsy

Michela Casella, Francesca Pizzamiglio, Antonio Dello Russo, Corrado Carbucicchio, Ghaliah Al-Mohani, Eleonora Russo, Pasquale Notarstefano, Maurizio Pieroni, Giulia D'Amati, Elena Sommariva, Marta Giovannardi, Andrea Carnevali, Stefania Riva, Gaetano Fassini, Fabrizio Tundo, Pasquale Santangeli, Luigi Di Biase, Leonardo Bolognese, Andrea Natale and Claudio Tondo

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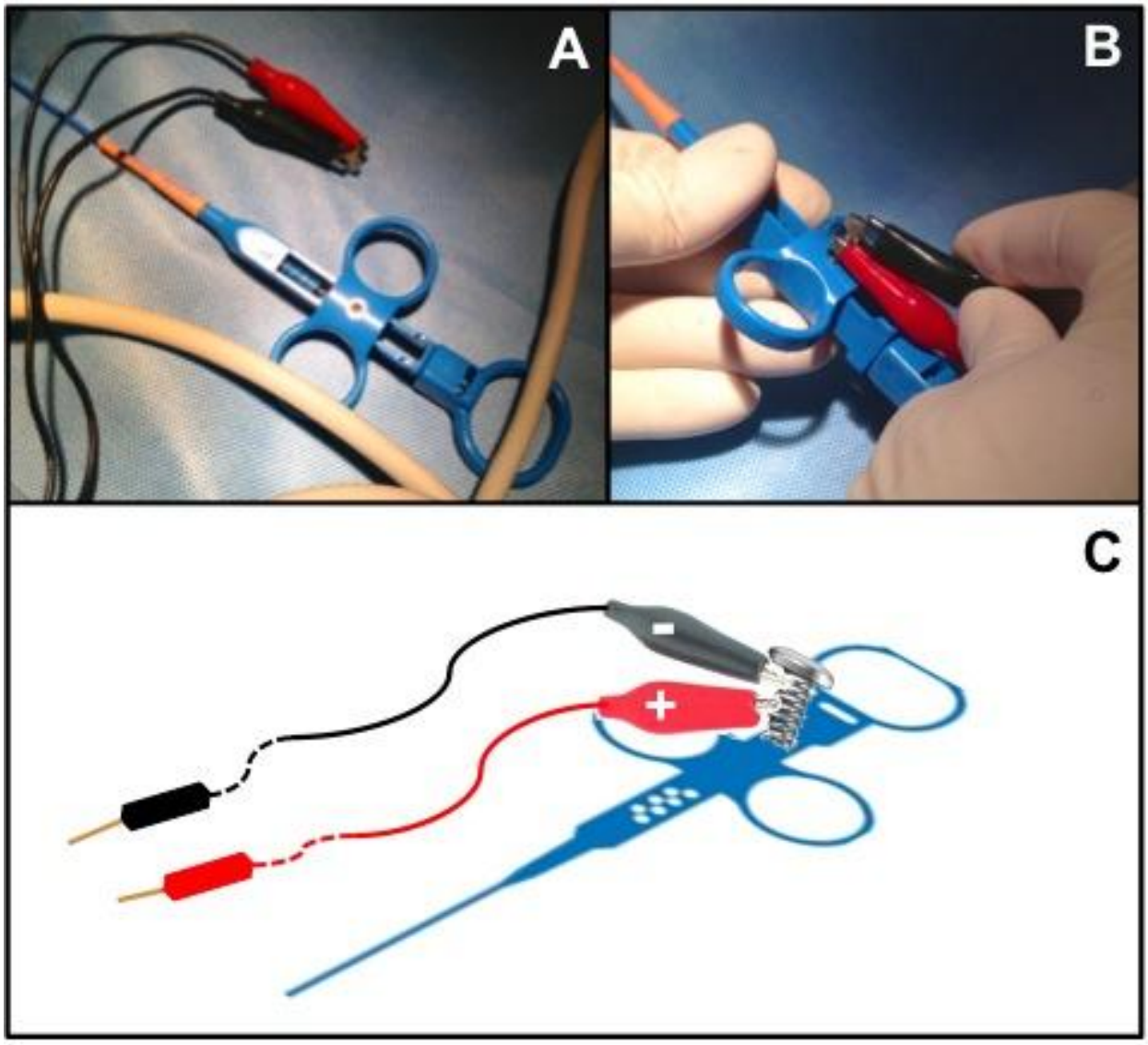
Supplemental Material

Supplemental Fig. 1



Panel A: The bioptome handle with its adapter and the small screw pinched with a couple of alligator clips. Red: positive pole; black: negative pole. Panel B: The small screw and the alligator clips are put into the handle adapter. Panel C: Sketch of the electrical network generated by the electric dipole.

Supplemental Table 1. Study population characteristics

Pt	Familial and Personal History		12-leads ECG		Ventricular arrhythmias		Two-dimensional echocardiography			Cardiac MRI			EMB results	Final Diagnosis
	Familiar disease evidence	Sudden death history	Conduction disorders	Repolarization abnormalities	PVC / NSVT	SVT	RV morpho-functional alterations	LV morpho-functional alterations	LV-EF	RV morpho-functional alterations	RV-EF	LV morpho-functional alterations		
1	0	0	0	1	1	0	1	0	60	1	20	0	fibro-fatty replacement; residual myocytes < 60%	ARVD/C
2	0	0	0	0	1	0	0	0	56	0	48	1	nonspecific findings	LV non-compaction
3	0	0	0	0	0	1	0	1	45	NA	NA	NA	mild hypertrophy and interstitial fibrosis	IDCM
4	1	1	0	0	0	1	1	0	61	1	42	1	mild hypertrophy and interstitial fibrosis	aspecific cardiac disease
5	0	0	1	0	1	0	0	0	61	1	39	1	cardiac mithocondrial proliferation	mithocondrial Disease
6	1	1	0	0	0	1	0	0	60	0	40	0	fibro-fatty replacement; residual myocytes 70%	ARVD/C
7	0	0	0	0	1	0	1	0	43	1	45	1	fibro-fatty replacement; residual myocytes < 60%	ARVD/C
8	0	0	0	1	0	0	0	0	60	0	45	0	nonspecific histological findings	idiopathic VF
9	0	0	0	0	1	0	0	0	55	1	48	0	inflammatory infiltrates associated with necrosis of adjacent myocytes	myocarditis

10	0	0	0	0	1	0	1	0	53	1	45	1	fibro-fatty replacement; residual myocytes 70%	ARVD/C
11	0	0	0	0	1	0	0	0	62	0	54	0	mild hypertrophy and interstitial fibrosis	idiopathic RVOT tachycardia
12	0	1	0	0	1	0	0	0	57	0	69	0	no pathological features	idiopathic RVOT tachycardia
13	0	0	0	0	1	0	0	1	31	1	40	1	widespread deposition of perinuclear lipofuscin pigment, mild interstitial edema	IDCM
14	0	0	0	0	1	1	0	0	62	0	53	0	no pathological features	idiopathic RVOT tachycardia
15	1	1	1	0	0	0	1	0	54	1	31	0	mild hypertrophy and interstitial fibrosis	aspecific cardiac disease
16	0	0	0	0	1	0	0	0	62	0	52	0	mild hypertrophy and interstitial fibrosis	idiopathic RVOT tachycardia
17	0	0	0	1	1	0	0	0	65	1	55	1	mild hypertrophy and interstitial fibrosis	previous myocarditis
18	0	0	1	0	0	1	1	0	45	0	45	1	mild hypertrophy and interstitial fibrosis	previous myocarditis
19	0	0	0	1	0	1	0	0	60	1	45	0	no pathological features	aspecific cardiac disease
20	0	0	0	1	1	0	1	0	66	1	40	1	fibro-fatty replacement; residual myocytes 70%	ARVD/C
21	0	0	0	0	1	0	0	0	56	0	51	0	no pathological features	idiopathic RVOT tachycardia

22	0	0	0	1	1	0	1	0	65	1	42	0	inflammatory infiltrates associated with necrosis of adjacent myocytes	myocarditis
23	0	0	0	1	0	1	1	1	50	1	40	1	non-necrotizing giant-cell granulomas surrounded by chronic flogistic infiltrate	sarcoidosis
24	0		0	0	1	0	0	0	65	1	57	0	no pathological features	idiopathic RVOT tachycardia
25	1	0	0	0	0	1	1	0	69	1	40	0	fibro-fatty replacement; residual myocytes 70%	ARVD/C
26	0	1	1	0	1	1	0	0	70	1	46	1	fibro-fatty replacement; residual myocytes < 60%	ARVD/C
27	0	0	0	0	1	1	0	0	65	1	53	1	fibro-fatty replacement; residual myocytes 70%	ARVD/C
28	0	0	0	1	0	1	0	0	70	1	46	1	fibro-fatty replacement; residual myocytes 70%	ARVD/C
29	0	1	0	1	1	0	1	0	60	1	58	0	inflammatory infiltrates associated with necrosis of adjacent myocytes	myocarditis

PVC: premature ventricular complex; NSVT: not sustained VT; SVT: sustained VT; EF: ejection fraction

Supplemental Table 2.

Pt	Site of withdrawal					Bipolar mapping	Characteristics of bipolar signals	Unipolar mapping	Biopsy findings							
	RVOT	septum	ant-lat	inf	apex	pathological 0/1	0 normal, 1 low-voltage, 2 fragmented, 3 double, 4 late	pathological 0/1	Suitable for analysis	ARVD	< ARVD	myocarditis	other	Hypertrophy / fibrosis	asp	npf
1	1					1	2	1	1	1						
		1				0	0	0	1							1
		1				0	0	0	1							1
	1					1	2	1	1	1						
2		1				0	0	0	1					1		
			1			0	0	0	1							1
			1			1	2	0	1						1	
				1		1	4	0	1						1	
3	1					1	3	1	1					1		
		1				0	0	0	0							
		1				0	0	0	0							
4					1	0	0	0	1					1		
		1				0	3	0	1					1		
		1				0	0	1	0							
5		1				0	0	0	0							
	1					1	1	1	1				**1**			
6		1				0	0	1	1		1					
		1				0	0	1	0							
7					1	1	2	1	1	1						
			1			0	0	0	1							1
			1			0	0	0	1							1
	1					1	2	1	1	1						
8	1					1	1	1	0							
		1				0	0	0	1						1	
		1				0	3	0	0							
9					1	0	0	0	1							1
			1			0	0	0	1			1				

			1			0	0	0	1			1				
10				1		1	1	0	1					1		
				1		1	1	0	1					1		
11		1				0	0	1	0							
					1	0	0	1	1		1					
12		1				0	0	0	1							1
		1				0	0	0	1							1
		1				0	0	0	1							1
13		1				1	1	1	1				**1**			
		1				0	0	0	0							
		1				1	1	1	0							
14		1				0	0	0	1							1
		1				0	0	0	0							
15		1				0	0	0	1							1
					1	0	0	0	1					1		
	1					0	0	1	1					1		
16		1				0	2	0	1					1		
		1				0	0	0	0							
		1				0	0	0	0							
17		1				0	0	0	1					1		
					1	0	3	0	1					1		
18		1				1	1	0	1					1		
			1			0	0	0	1					1		
19		1				0	0	0	0							
		1				0	0	0	1							1
20					1	0	0	1	1		1					
		1				0	2	0	1					1		
		1				0	0	1	1		1					
21		1				0	0	0	1							1
		1				0	0	0	0							
		1				0	0	0	0							
22		1				0	0	0	1							1
					1	0	0	0	1			1				
			1			0	0	0	1			1				
23			1			0	0	1	0							
			1			1	2	0	0							

			1			0	2	1	1				**1**			
				1		0	3	0	1							1
24		1				0	0	0	1							1
		1				0	4	0	1							1
25				1		1	1	0	1					1		
		1				0	0	1	1		1					
26					1	0	0	0	1						1	
			1			1	1	1	1	1						
			1			1	1	1	1	1						
27	1					0	0	1	1		1					
28					1	0	0	1	1		1					
			1			0	0	0	0							
			1			0	0	1	0							
29		1				0	0	0	1			1				
		1				0	0	0	1			1				
					1	0	0	1	1							1
					1	0	0	1	1							1
	8	40	15	5	12	18		27	60	6	7	6	**3**	15	4	19

RVOT: right ventricle outflow tract; ant-lat: antero-lateral wall; inf: inferior wall; ARVD: arrhythmogenic right ventricle dysplasia; < ARVD: minor criteria for ARVD diagnosis; myo: myocarditis; asp: aspecific; npf: no pathological findings

Normal electrograms: electrograms with 3 or fewer sharp and discrete deflections from baseline, amplitude >1.5 mV, duration <70 ms, and/or ratio amplitude/duration ≥0.046;

Low-voltage electrograms: electrograms with 3 or fewer sharp and discrete deflections from baseline, amplitude ≤1.5 mV, duration < 100 ms;

Fragmented electrograms: electrograms characterized by multiple (>3) discrete deflections, amplitude ≤1.5 mV, and a duration >100 ms;

Double potentials: electrograms defined as any discrete deflection, either single or multiple, separated by an isoelectric signal of > 20 ms from the local ventricular electrogram (bipolar);

Late potentials: any electrogram with an isolated component occurring ≥100 ms after the QRS complex of the surface ECG (lead V1).

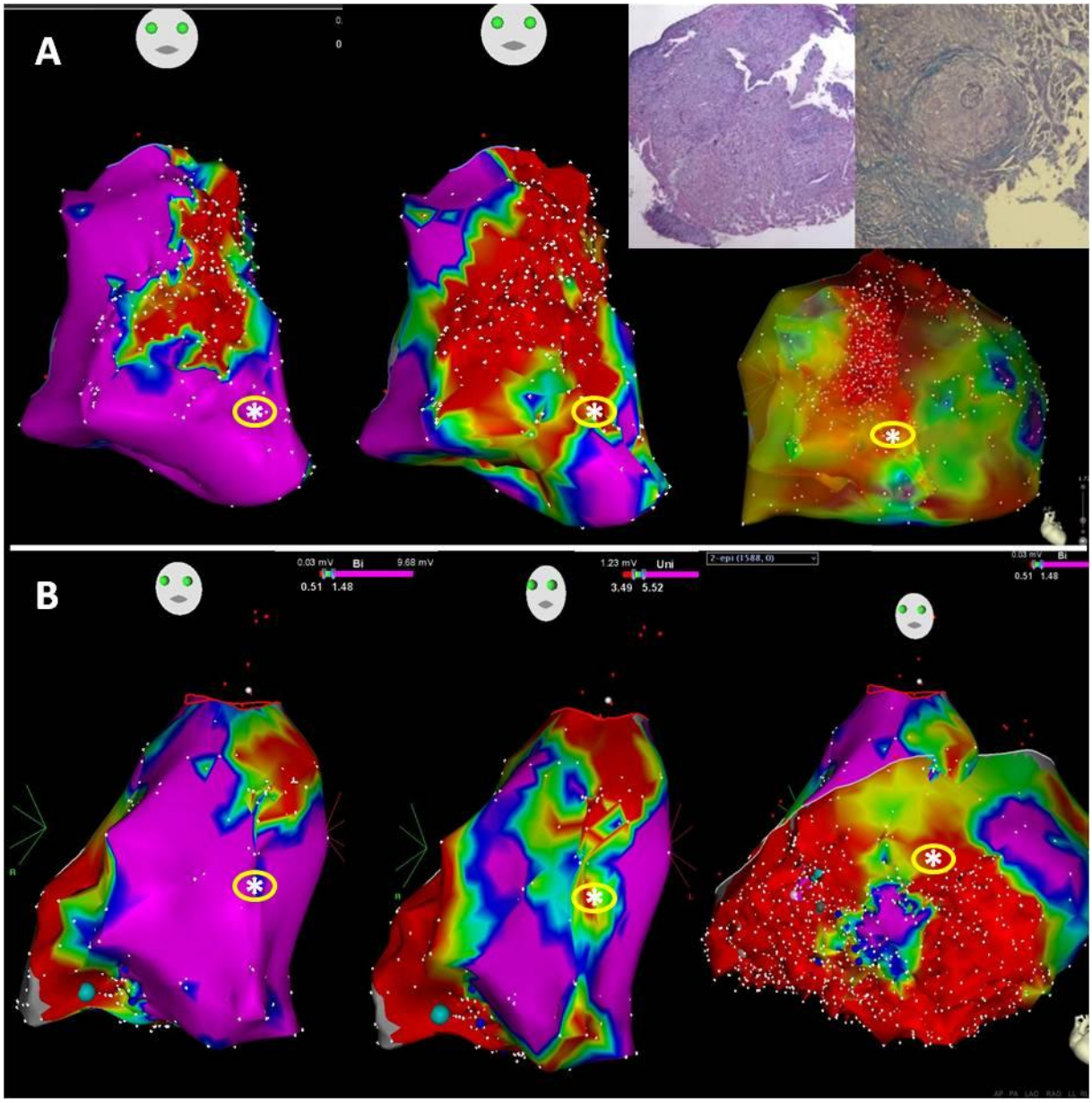
Supplemental Results

Epicardial Electroanatomic Voltage Mapping

In five patients, we performed an epicardial mapping by a percutaneous subxiphoid access.

Considering the biopsy site we observed that: concordant bipolar and unipolar normal voltages at endocardial EVM corresponded to a normal bipolar epicardial mapping and normal EMB in two cases; concordant bipolar/unipolar low-voltages at endocardial EVM corresponded to a low-voltage bipolar epicardial mapping and EMB features diagnostic for idiopathic dilated cardiomyopathy in one case; finally, in the remaining two patients (sarcoidosis and ARVD/C patients), the discordant bipolar normal voltage and unipolar low-voltage at endocardial EVM corresponded to an area of bipolar low-voltages at epicardial mapping (Supplemental Fig 2).

Supplemental Fig 2



Panel A: endocardial bipolar (left), endocardial unipolar (middle) and epicardial bipolar map (right) of a patients with a bioptic diagnosis of cardiac sarcoidosis.

In the box, histological findings that confirmed the diagnosis of sarcoidosis: non-necrotizing giant-cell granulomas surrounded by chronic flogistic infiltrate. Granulomas are made up of CD68+ macrophages and the flogistic infiltrate of CD3+ lymphocytes.

Panel B: endocardial bipolar (left), endocardial unipolar (middle) and epicardial bipolar (right) maps of a patient undergoing EMB for a suspicion of ARVD/C.

The asterisks on the maps indicate the area where myocardial samples were drawn from. In both cases, we observed a visual correlation between the abnormal voltage areas in the endocardial unipolar and epicardial bipolar maps in terms of both overall size and matching anatomic location.

Movie 1

Movie 1 shows the correct position of the bioptome checked through the CARTO system and through ICE.